Implications of
PRESERVING LONG-TERM RENAL FUNCTION
After Renal Transplantation

Presented by:

National Institute of Allergy and Infectious Diseases of
the National Institutes of Health
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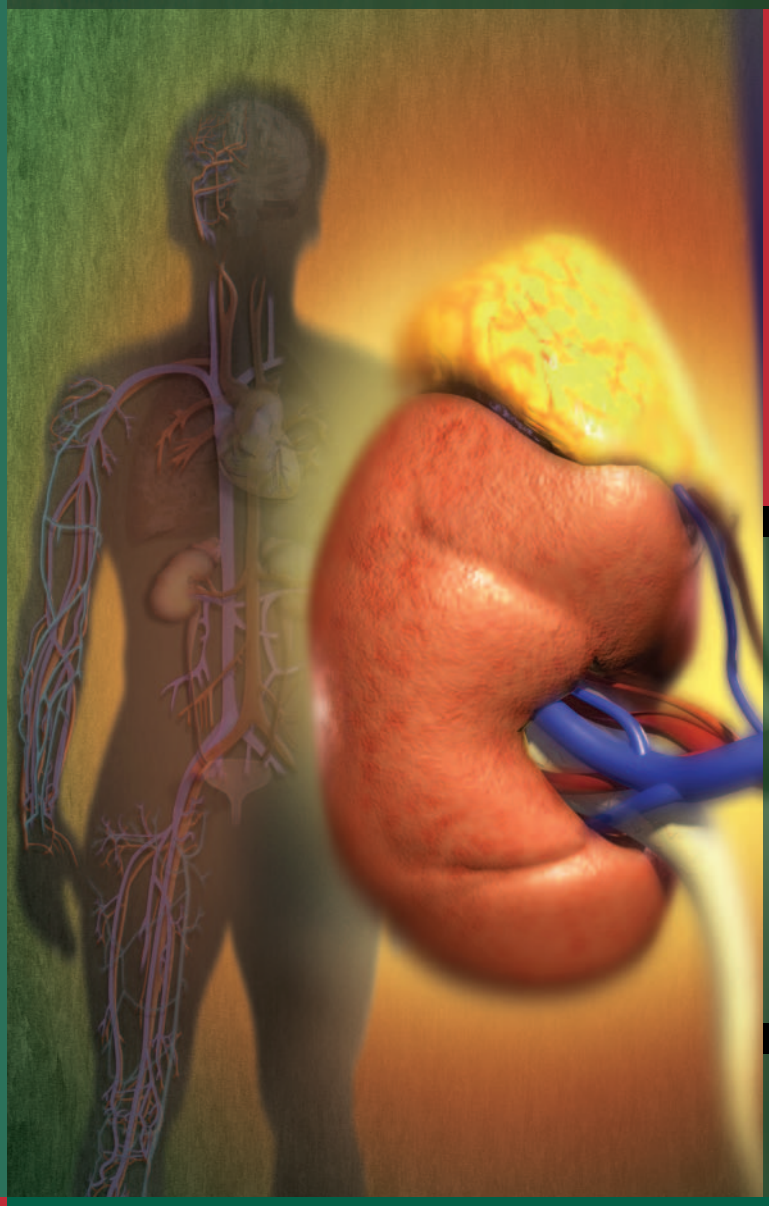

Based on a Roundtable

Held November 11, 2003

in Bethesda, Maryland

In Cooperation With:

- American Society of Transplant Surgeons
- United Network for Organ Sharing
- North American Transplant Coordinators Organization
- International Transplant Nurses Society

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Dear Colleague:

We are pleased to provide you with this continuing medical education newsletter, *Implications for Preserving Long-Term Renal Function After Renal Transplantation*. This newsletter has been developed as an overview from the proceedings of a roundtable meeting presented by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, US Department of Health and Human Services, held November 2003 in Bethesda, Maryland.

As you know from your clinical practice, the primary cause of death in renal transplant recipients is cardiovascular disease. Although 1-year graft function is a potent predictor of patient and graft survival, other powerful traditional risk factors, such as age, gender, race, diabetes mellitus (both before and after transplantation), hypertension, obesity, and immunosuppressive regimens, come into play in the multifactorial risk pattern underlying the development of cardiovascular disease. In addition to these traditional risk factors, recent research points to the role of nontraditional risk factors, such as C-reactive protein, homocysteine, and hyperleptinemia, in the development of posttransplant cardiovascular disease.

The objective of this newsletter is to present to clinicians the most recent research findings on these critical risk factors and on the management and/or correction of modifiable risk factors in the posttransplant renal population. It is known that such modifiable risk factors, including anemia, hyperlipidemia, and hypertension, are often underdiagnosed. This newsletter will provide the research and treatment strategies to enable the clinician to optimally manage the renal transplant recipient such that the burden of cardiovascular disease in this patient population may be significantly reduced over time, with improved long-term patient survival.

This educational activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Minnesota Office of Continuing Medical Education and SynerMed® Communications. It was developed in cooperation with the American Society of Transplant Surgeons, the International Transplant Nurses Society, the North American Transplant Coordinators Organization, and the United Network for Organ Sharing, and has been supported by an unrestricted educational grant from Wyeth. This newsletter also is posted on the Medscape® website (www.medscape.com).

We are confident that you will find this newsletter a valuable resource in developing and participating in optimal management strategies for your renal transplant recipients.

Sincerely,

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IMPLICATIONS FOR PRESERVING LONG-TERM RENAL FUNCTION AFTER RENAL TRANSPLANTATION

INTRODUCTION

Cardiovascular disease represents the leading cause of death in patients with chronic kidney disease.[1] Moreover, progression of chronic renal insufficiency (CRI) to end-stage renal disease (ESRD) is accompanied by a dramatic increase in the incidence of cardiovascular disease despite intensive treatment.

To characterize the risk factors involved in chronic kidney disease progression and cardiovascular disease development more precisely, the multicenter Chronic Renal Insufficiency Cohort (CRIC) Study is examining and following up approximately 3000 patients with chronic renal insufficiency (glomerular filtration rate [GFR] <60 mL/min). The study participants, who reflect the racial, ethnic, and gender composition of the US ESRD population, will be monitored for 5 years. Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, the CRIC Study seeks to identify high-risk subgroups and potential etiologic factors to guide the development of therapeutic interventions for reducing the burden of advanced renal failure and its associated cardiovascular mortality.[2]

Kidney transplant recipients also constitute a population at particularly high risk. Prior to transplantation, ESRD patients suffer a number of important comorbidities, including diabetes and hypertension, that increase their risk of cardiovascular disease. Accordingly, it seems logical that introduction of therapeutic strategies that might minimize, or at least not compound, this risk would be especially important.

Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients

Statement of Need

Approximately 8 million Americans suffer with chronic kidney disease, as characterized by glomerular filtration rates below 60 mL/min for 3 months or more.[3] Renal dysfunction is associated with an increased risk of fatal and nonfatal acute myocardial infarction, stroke, and hospitalization for congestive heart failure. Moreover, progression of chronic renal insufficiency to end-stage renal disease, despite intensive treatment, is often accompanied by a dramatic increase in cardiovascular events.

To determine more precisely the risk factors for rapid decline in kidney function and development of cardiovascular disease, the landmark Chronic Renal Insufficiency Cohort Study is examining and following up on approximately 3000 patients with chronic renal insufficiency. Also significant is the additional risk burden on recipients of kidney transplants. An analysis of registry data suggests a trend toward lower serum creatinine concentrations, as well as a reduced incidence of acute rejection, among recent renal transplant recipients. However, available results have not yet suggested improvement in long-term outcomes. Newer approaches to immunosuppression may reduce the risk of chronic allograft nephropathy and perhaps cardiovascular events in this population. It is important for all members of the renal transplant team to be aware of the additional risks faced by their patients and of potential means to minimize the effects of those risks.

In November 2003, a scientific roundtable, presented by the National Institute of Allergy and Infectious Diseases, brought together a group of internationally recognized experts in transplantation medicine to review the relationship between renal dysfunction and cardiovascular disease in both the general and transplant populations. The importance of long-term preservation of renal function in kidney transplant recipients was discussed, including the use of calcineurin inhibitor–sparing and steroid-sparing immunosuppressive protocols as a potential therapeutic approach.

This newsletter summarizes the findings from this roundtable meeting and their implications for medical specialists in the field of kidney transplantation. This newsletter is part of a series of educational publications addressing these timely issues.

EPIDEMIOLOGY OF RENAL DYSFUNCTION AND ITS RAMIFICATIONS FOR CARDIOVASCULAR DISEASE IN THE GENERAL POPULATION

"...Even a moderate level of renal dysfunction is a major harbinger of significant cardiovascular disease...."

Akinlolu O. Ojo, MD, PhD

To identify strategies for preserving long-term renal function in kidney transplant recipients, it is instructive to look at the paradigm of renal dysfunction and cardiovascular disease in the general population, accepting the premise that many cardiovascular disease risk factors are similar in the 2 populations.

To understand how to preserve renal function, it is important to define chronic renal dysfunction. The National Kidney Foundation defines kidney disease at a structural level; that is, kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. The Kidney Disease Outcomes Quality Initiative defines the disease based on the level of renal function, ie, GFR <60 mL/min for ≥3 months.[1] Either definition is sufficient for classifying a patient as having kidney disease; however, the second definition is more relevant to our understanding of what constitutes clinically significant kidney disease.

EDUCATIONAL OBJECTIVES

After reading this newsletter, participants should be able to:

- Discuss cardiovascular risk factors among renal transplant recipients, including long-term renal dysfunction
- Describe the importance of preserving long-term renal function
- Discuss the mechanisms of chronic renal allograft nephropathy and cardiovascular disease
- Describe immunosuppressive protocols, including calcineurin inhibitor–sparing and steroid-sparing immunosuppressive protocols, and their effect on optimal long-term renal function

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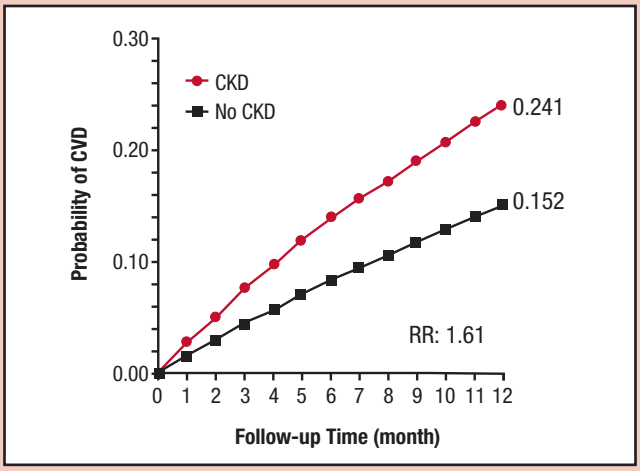
Evidence suggesting a relationship between significant kidney disease and a high incidence of cardiovascular disease comes from the United States Renal Data System (USRDS). In their 1-year study of Medicare patients ≥67 years of age, the incidence of cardiovascular disease among those with chronic kidney disease was 24%, compared with 15% among those not diagnosed with chronic kidney disease (Figure 1).[4]

Additional evidence that persons with chronic kidney disease are at higher risk for cardiovascular disease can be gathered from results of the Heart Outcomes Prevention Evaluation (HOPE) study, a multinational study enrolling approximately 9300 patients ≥55 years of age with diabetes or vascular disease and one additional cardiovascular disease risk factor (eg, hypertension, obesity). The impact of chronic renal insufficiency on cardiovascular events was evaluated in a post hoc analysis. Patients were divided into 2 groups based on their serum creatinine (SCr) levels: ≥1.4 mg/dL (n=980) or <1.4 mg/dL (n=8307). They were then followed for ≥3 years; a clear association was seen between renal insufficiency and the occurrence of at least one major cardiovascular outcome (myocardial infarction [MI], stroke, cardiovascular death, hospitalization for congestive heart failure, or revascularization). In fact, the incidence of each of these outcomes was approximately 60% higher among patients with renal insufficiency than among those without renal insufficiency (Table 1). The investigators concluded that in this patient population, mild renal insufficiency significantly increased the risk of subsequent cardiovascular events.[5]

The Cooperative Cardiovascular Project studied the impact of renal dysfunction on post–acute MI mortality in a Medicare population of persons aged ≥65 years. Patients who experienced acute MIs were assigned to 1 of 3 groups based on SCr levels: <1.5 mg/dL (no renal insufficiency), 1.5-2.4 mg/dL (mild insufficiency), or 2.5-3.9 mg/dL (moderate insufficiency). At 1 year, there was a 24% mortality rate among patients with no renal insufficiency. Among those with mild or moderate renal insufficiency, mortality rates were 46% and 66%, respectively (P<.001). Almost 3 times as many patients with moderate renal insufficiency died as those without renal insufficiency. Of interest was the observation that 1-month mortality for patients with

FIGURE 1

PROBABILITY OF CARDIOVASCULAR DISEASE (CVD) IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)



Adapted from USRDS 2003.

TABLE 1

CARDIOVASCULAR OUTCOMES IN PATIENTS WITH AND WITHOUT CHRONIC RENAL INSUFFICIENCY (CRI)

Outcome	CRI (n=980) %	No CRI (n=8307) %	*P*
MI	16.3	10.5	<.001
Stroke	5.0	4.0	.07
Cardiovascular death	11.4	6.6	<.001
All death	17.8	10.6	<.001
Hospitalized for congestive heart failure	6.0	2.9	.0115
Revascularization	19.6	16.9	.08

Adapted with permission from Mann JF, et al. *Ann Intern Med*. 2001; 134:629-636.

no renal insufficiency was 13%, compared with 44% for those with moderate insufficiency. These results suggest that renal insufficiency is a risk factor for cardiovascular disease independent of traditional risk factors.[6]

Several other studies have reported similar findings. For example, in the Hypertension Detection and Follow-up Program, SCr levels >1.7 mg/dL were associated with a 2.2-fold higher adjusted odds ratio for death at 8 years.[7] For women in the Framingham Heart Study, elevated SCr levels were associated with a 2-fold higher risk of death.[8] The Hypertension Optimal Treatment Study showed an association between elevated SCr levels and higher mortality risk.[9] Importantly, all of these studies adjusted for other cardiovascular risk factors and revealed an independent effect of chronic renal insufficiency on mortality risk.

If such statistics are applied to the approximately 8 million people in the United States considered to have chronic kidney disease, close to 2 million of them would have experienced at least one significant cardiovascular event over a 1-year period, and the majority of people with chronic kidney disease will likely die of cardiovascular disease.[4] If this hypothesis is correct, cardiovascular disease poses a more immediate threat of mortality to patients with renal insufficiency than does ESRD. Although some of the ESRD seen in patients with chronic renal insufficiency is due to traditional risk factors, these factors cannot account entirely for the development of ESRD. Similarly, the higher prevalence of cardiovascular disease among patients with chronic renal insufficiency is not entirely attributable to traditional risk factors.[10,11]

We do not have a clear understanding of the progression of renal function decline, of how to preserve renal function, or of a precise and practical method to measure it. In the CRIC Study, serial echocardiograms, electrocardiograms, and coronary electron beam or spiral computed tomograms are being obtained for each participant. In addition, GFR and a host of biochemical parameters are being measured serially. Ideally, this study will provide better tools for measuring renal function and offer more insight into the relationship between cardiovascular disease and chronic renal insufficiency in the general population. An important next step would be to design a similar study for the renal transplant population.

DO MILD TO MODERATE DECLINES IN RENAL FUNCTION CONTRIBUTE TO CARDIOVASCULAR DISEASE RISK?

"The majority of evidence now supports the idea that renal insufficiency contributes to and exacerbates many cardiovascular risk factors."

Bertram L. Kasiske, MD

The finding that individuals with renal insufficiency appear to have a higher risk of developing cardiovascular disease leads one to ask whether cardiovascular risk factors may actually contribute to kidney damage. Reliable evidence from randomized trials suggests that hypertension causes kidney disease. Dyslipidemia also may affect the kidney adversely. It is plausible that the cause-and-effect relationship is bidirectional, so that hypertension and dyslipidemia can be viewed as consequences of chronic kidney disease.

Hypertension

One of the strongest risk factors for cardiovascular disease is elevated blood pressure. Both the Third National Health and Nutrition Examination Survey (NHANES III) and the Framingham Heart Study suggested that renal dysfunction contributes to hypertension. NHANES III reported that 70% of noninstitutionalized individuals in the United States with renal dysfunction (defined as SCr levels ≥1.6 mg/dL in men and ≥1.4 mg/dL in women) have hypertension. In the Framingham Study, there also was a significant association between elevated SCr levels and hypertension.[12,13]

Mechanisms driving mild to moderate renal dysfunction and hypertension have been linked to the metabolic syndrome and obesity.[14] It is also thought that activity of the sympathetic nervous system is increased in patients with renal insufficiency and that this may contribute to hypertension.[15] Leptin is a mediator that also may link hypertension to renal insufficiency. Leptin levels, which are high in patients with renal insufficiency,[16] also correlate significantly with elevated triglyceride levels and low levels of high-density lipoprotein cholesterol (HDL), typical patterns of the metabolic syndrome.[17] Other mediators may also play a role and are currently being investigated.

Dyslipidemia

A few published studies suggest that there is a link between lipid abnormalities and mild to moderate renal insufficiency. In a cross-sectional study of patients with hypertension who were classified as having either normal or decreased creatinine clearance (Cr_{Cl}) (30-89 mL/min), there were no differences in total cholesterol, HDL, or low-density lipoprotein cholesterol (LDL), a nonsignificant increase in triglyceride levels, but a significant increase in lipoprotein (a) levels, in those with renal insufficiency.[18] As part of the Heart and Estrogen-Progestin Replacement Study, postmenopausal women with known coronary heart disease were divided into 3 groups based on their SCr levels. Data analysis revealed that several cardiovascular risk factors, including hypertension ($P<.001$) and elevated triglyceride ($P=.002$) and lipoprotein (a) levels ($P=.05$), were associated with elevated SCr levels.[19]

C-Reactive Protein

Cardiovascular disease also is affected by the microinflammatory environment, in which an elevation in markers of inflammation, such as C-reactive protein (CRP), occurs. Recent studies suggest that renal insufficiency may contribute to increases in CRP or other markers of inflammation. Panichi and colleagues showed strong correlations between mild renal insufficiency and elevations in levels of both CRP and interleukin-6 ($P<.0001$ for both).[20] The Dutch Prevention of Renal and Vascular End-Stage Disease Study, which included more than 7000 nondiabetic patients, showed that the odds of having a decrease in estimated Cr_{Cl} rose with each increasing quartile of CRP increase, independent of other risk factors.[21] Similarly, in a study by Stam and colleagues, the degree of Cr_{Cl} correlated highly with elevations in CRP, even with mild to moderate declines in GFR.[22] There were also positive correlations with von Willebrand's factor, another marker of endothelial dysfunction.

Uric Acid

It is well known that renal dysfunction and insufficiency are associated with elevations in uric acid levels, although it remains unclear whether elevated uric acid is actually a cardiovascular disease risk factor.[23,24] Increases in uric acid are thought to occur at the tubular level. Cappuccio and colleagues demonstrated that tubular function, measured as fractional excretion of sodium and of lithium (a surrogate marker for sodium handling in the proximal tubule), changed with serum uric acid levels.[25] This suggests another potential mechanism for a contribution of renal dysfunction to cardiovascular disease.

Insulin Resistance

The kidney is usually not viewed as a metabolic organ; however, it appears to have an essential role in glucose homeostasis and insulin resistance.[26] Indeed, during fasting, the kidney contributes as much to plasma glucose levels as the liver.

Evidence that renal function plays a role in glucose tolerance can be found in a study that evaluated 227 patients with never-treated essential hypertension. In this study, the rate of age-associated decline in GFR was higher in those with impaired glucose tolerance than in those with normal glucose tolerance.[27]

If renal insufficiency causes abnormalities in glucose homeostasis and insulin sensitivity, it probably affects a number of other cardiovascular risk factors, as indicated by data from NHANES II, shown in Table 2. In this study, reductions in estimated GFR correlated significantly with elevations in systolic blood pressure ($P<.001$), total cholesterol ($P<.001$), body mass index ($P<.001$), percentage of subjects with diabetes ($P=.006$),[28] suggesting a role for chronic renal insufficiency in the development of the metabolic syndrome.

Parathyroid Hormone

Both elevated parathyroid hormone levels and the concomitant reductions in vitamin D have been implicated as cardiovascular risk factors. One study concluded that hyperparathyroidism is strongly linked to cardiovascular disease.[29] An earlier study demonstrated that mild to moderate reductions in renal function were associated with elevated parathyroid hormone and reduced vitamin D concentrations.[30] These results were confirmed in another study, which showed that parathyroid hormone levels rose and vitamin D levels dropped with only modest declines in renal function,[31] suggesting that renal insufficiency may potentiate these cardiovascular risk factors.

Homocysteine

Although not proven to be a causative factor in cardiovascular disease, homocysteine is elevated in the presence of renal dysfunction. Controlled trials are under way to establish the role of homocysteine in cardiovascular disease risk.

Figure 2 shows the complicated relationships between renal function and cardiovascular risk factors. Again, many of these relationships are probably bidirectional, and the majority of evidence now supports the theory that renal insufficiency contributes to and exacerbates cardiovascular risk.

THE BANFF CLASSIFICATION: STANDARDS FOR BIOPSY IDENTIFICATION OF CAUSES OF POSTTRANSPLANT RENAL DYSFUNCTION

"The Banff Classification is based on a scoring system that looks at all aspects of the biopsy specimen, not just rejection. Many markers are quantitated to identify the severity of rejection, as there is no longer a single marker of rejection."

Kim Solez, MD

Because causes of posttransplant renal dysfunction are difficult to assess, and different entities are treated with very different approaches, ensuring optimal patient and graft survival following kidney transplantation is particularly challenging. Accurate determination of causes of renal dysfunction is critical, because misdiagnosis could be life-threatening to a transplant recipient. In an attempt to provide more accurate diagnosis and rigorous quantitation, an international classification for the evaluation of percutaneous renal biopsy specimens—the Banff Classification—was created in the 1990s. The latest version of this classification, known as Banff '97, has been highly successful in guiding therapy and predicting outcomes during the early posttransplant period, the period during which acute rejection is most likely to occur. The goal is to fully extend the usefulness of the classification to the late engraftment phase and for biopsy specimens

TABLE 2

RELATIONSHIP BETWEEN GLOMERULAR FILTRATION RATE (GFR) AND CARDIOVASCULAR DISEASE

Baseline Characteristics	Est GFR ≥90 mL/min (n=4959)	Est GFR 70-89 mL/min (n=1068)	Est GFR <70 mL/min (n=327)	*P*
Systolic blood pressure (mm Hg)	128	131	143	<.001
Total cholesterol (mg/dL)	221	230	239	<.001
Body mass index (kg/m^2)	25.7	26.1	27.1	<.001
Diabetes (%)	4.5	6.5	8.5	.006

Est = estimate.

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obtained during this period to be as useful in clinical management as during the early period. Banff '97 uses histologic "types" rather than continuous "grades" of rejection.[32]

Diagnosing and Categorizing Rejection

The Banff '97 diagnostic categories for renal allograft biopsies are shown in Table 3. The primary criteria for rejection are tubulitis and arteritis; other criteria include interstitial inflammation and glomerulitis. Acute/active rejection and chronic/sclerosing allograft nephropathy (preferred over the term "chronic rejection," which may not account for all possible causes of allograft damage) are graded based on the number and extent of criteria present.[32]

Important Points About the Banff Classification

There are a number of non–rejection-related factors that may cause changes in biopsy specimens and that should be considered in a differential diagnosis (Table 4, page 6). Particular attention should be paid to ruling out posttransplant lymphoproliferative disorder, which often coexists with rejection and can complicate diagnosis and treatment.[32] In making treatment decisions for allograft recipients, it is important that physicians never rely solely on the results of biopsies but also take into consideration all pertinent factors, including patient characteristics and history. Central slide review based on the Banff Classification is an important element in ensuring accuracy of biopsy rejection diagnosis endpoints in clinical trials of new antirejection agents and strategies.

CARDIOVASCULAR DISEASE: UNIQUE MECHANISMS IN RENAL TRANSPLANT RECIPIENTS

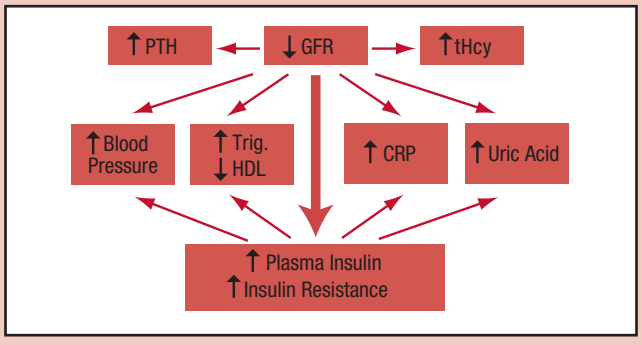
"Both anemia and immunosuppression appear to influence the incidence of cardiovascular disease in renal transplant recipients. It is more critical than ever that patients be carefully evaluated posttransplantation to help reduce such risks."

Donald E. Hricik, MD

Although cardiovascular morbidity and mortality are much more prevalent among patients on dialysis than among renal transplant recipients, the cardiovascular mortality rate for transplant recipients is nearly double that observed in the general population (Figure 3, page 7).[33] The higher incidence is due, in part, to impaired GFR. Additional contributing factors are thought to be anemia and immunosuppression, which are discussed next.

FIGURE 2

THE KIDNEY AND ITS RELATIONSHIP TO CARDIOVASCULAR DISEASE



Anemia

Anemia may be one of the most important nontraditional cardiovascular disease risk factors among patients with chronic kidney disease, but it is often overlooked. Evidence indicates that anemia contributes to left ventricular hypertrophy and, ultimately, to heart failure in patients with chronic kidney disease. The influence of anemia on the development of left ventricular hypertrophy may be even more important than that of systolic blood pressure.[34]

TABLE 3

BANFF '97 DIAGNOSTIC CATEGORIES FOR RENAL ALLOGRAFT BIOPSIES

1. Normal

2. Antibody-mediated rejection
Rejection demonstrated to be due, at least in part, to anti-donor antibody
A. Immediate (hyperacute)
B. Delayed (accelerated acute)

3. Borderline changes: "Suspicious" for acute rejection
This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and at least i1

4. Acute/active rejection

Type (Grade)	Histopathological findings
IA	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells)
IB	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross section or group of 10 tubular cells)
IIA	Cases with mild to moderate intimal arteritis (v1)
IIB	Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphatic inflammation)

5. Chronic/sclerosing allograft nephropathy

Grade	Histopathological findings
Grade I (mild)	Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection
Grade II (moderate)	Moderate interstitial fibrosis and tubular atrophy (a) or (b)
Grade III (severe)	Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)

6. Other — Changes not considered to be due to rejection

Adapted with permission from Racusen LC, et al. *Am J Transplantation*. 2003;3:708-714.

TABLE 4

OTHER NONREJECTION DIAGNOSES IN RENAL ALLOGRAFT BIOPSIES

- Posttransplant lymphoproliferative disorder
- Nonspecific changes
  - focal interstitial inflammation without tubulitis
  - reactive vascular changes
  - venulitis
- Acute tubular changes
- Acute interstitial nephritis
- Cyclosporine- or tacrolimus-associated changes, acute or chronic
- Subcapsular injury
  - "healing in"
- Pretransplant acute endothelial injury
- Papillary necrosis
- *De novo* glomerulonephritis
- Recurrent disease
  - immune complex glomerulonephritis
  - focal segmental glomerulosclerosis
  - diabetes
  - hemolytic-uremic syndrome
  - other
- Preexisting disease
- Viral infection
- Obstruction/reflux, urine leak
- Other

Racusen LC, et al. The Banff '97 working classification of renal allograft pathology. *Kidney Int.* 1999;55(2):713-723.

There is growing evidence that the incidence of anemia in renal transplant recipients, particularly several years posttransplantation, is increasing, possibly generating a larger cardiovascular disease burden. For example, in one multicenter, cross-sectional study involving 4263 renal transplant recipients, the incidence of anemia at 12 months posttransplantation was 38.6%. There was an inverse relationship between hemoglobin levels and number of rejection episodes.[35]

Anemia is a significant cardiovascular risk factor, particularly in a high-risk population such as recent renal transplant recipients.[36] It is unknown whether more aggressive management of anemia may help reduce the risk of cardiovascular events for these patients.

Immunosuppression

Although there is no direct evidence that immunosuppressive drugs enhance cardiovascular risk and thus contribute to patient mortality, indirect evidence suggests that they may. For example, the prevalence of hypertension is high in transplant recipients, and hypertension has been associated with a negative impact on graft function and even on graft survival.[37] It is also known that some immunosuppressants adversely affect blood pressure and promote hypertension, as shown in Table 5.

Immunosuppressive agents may also contribute to the development of posttransplant diabetes mellitus (PTDM), the incidence of which appears to be increasing and which may affect graft survival negatively. PTDM has been attributed to the use of steroids; however, calcineurin inhibitors now appear to play a role as well. In fact, since these agents were introduced, the incidence of PTDM has gradually increased. For example, tacrolimus use may increase the risk of PTDM.[38] African Americans who receive tacrolimus-based immunosuppression appear to have the highest incidence of PTDM (36%, vs 15% of Caucasians who receive the same regimen).[39]

Immunosuppressants also appear to affect the incidence of hyperlipidemia. Cyclosporine may increase the production of very low-density lipoprotein precursors and decrease bile synthesis and secretion, leading to the retention of cholesterol.[40,41] Some target-of-rapamycin (TOR) inhibitors also increase hepatic synthesis of triglycerides and secretion of very low-density lipoproteins.[42]

Cumulative data suggest that the drugs used to reduce transplant rejection–risk and pathogenicity also contribute to cardiovascular disease–related processes. In addition, anemia appears to influence the incidence of cardiovascular disease in renal transplant recipients, as shown in Figure 4. As patients live longer, it is critical that they be carefully evaluated posttransplantation to help reduce these risks.

RENAL FUNCTION AND CARDIOVASCULAR DISEASE FOLLOWING RENAL TRANSPLANTATION

"Time on dialysis, independent of diabetes or hypertension, is also a strong risk factor for cardiovascular death, suggesting that renal failure is more deleterious than may have been predicted, and its severity impacts overall survival."

Bruce Kaplan, MD

Cardiovascular disease risk in renal transplant recipients is significantly lower in patients who have undergone renal transplantation than in patients with ESRD who remain on a transplant waiting list. That survival advantage is reflected in an increased life expectancy and decreased mortality, primarily as a result of cardiovascular events.[43,44] Thus, transplantation offers survival advantages over maintenance dialysis.

To assess the impact of renal function on cardiovascular mortality following renal transplantation, a retrospective analysis was conducted of 58,900 adult patients registered in the USRDS who received primary renal transplants between 1988 and 1998 and who had ≥1 year of graft survival. The patients were divided into 7 groups according to SCr at 1 year posttransplantation.[45] Multivariate analyses were used to correct for demographics, cause and time of ESRD, immunosuppressive regimens, delayed graft function, and acute rejection. The primary endpoint was cardiovascular death beyond 1 year of transplantation. Cardiovascular death while the patient had a functioning graft was investigated separately from all cardiovascular death, including death following graft loss.

Overall, there were nearly 6000 deaths, of which almost 1800 were attributed to cardiovascular causes. Cerebrovascular deaths were not

included as cardiovascular deaths; if they had been, the overall cardiovascular-related death rate would have been approximately 40%.[46] There was a trend toward a higher mortality risk following graft loss.

Cox proportional hazard analysis revealed that several pretransplant factors increased cardiovascular mortality risk, among them recipient age and ESRD. Importantly, hypertension and diabetes were associated with the greatest risk of posttransplant cardiovascular death. Time on dialysis, independent of diabetes or hypertension, was also a strong risk factor for cardiovascular death, suggesting that renal failure is more deleterious than may have been predicted and that its severity impacts overall survival.

The results of this study indicate that the survival advantage of renal transplantation is likely associated with kidney function, a factor that also applies to patients on dialysis, as well as to those who return to dialysis after graft failure. Following transplantation, the ultimate goal is to delay deterioration of renal function, prevent the need for retransplantation, and increase overall patient survival. Although renal function stabilizes in a majority of patients for several years after transplantation, current information indicates that decline is inevitable for the vast majority of individuals over time. Thus, early interventions to prevent further reductions in renal function are clearly desirable.

RENAL FUNCTION AS A PREDICTOR OF GRAFT AND PATIENT SURVIVAL

"Serum creatinine remains one of the most critical and possibly one of the most important variables in assessing the risk of graft loss, patient death, and cardiovascular death."

Bruce Kaplan, MD

Recognizing the importance of renal function to long-term graft and patient survival after renal transplantation, it is important to determine whether renal function is a reliable surrogate marker for allograft loss.

TABLE 5

SIDE EFFECTS OF IMMUNOSUPPRESSIVE AGENTS

	CsA	Tac	Srl	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal insufficiency	++	++	∅	∅	∅
Hyperlipidemia	++	+	++	++	∅
Hyperkalemia	+++	+++	∅	∅	∅
Tremor	∅	+	∅	∅	∅
Hirsutism	+	∅	∅	∅	∅
Gingival hyperplasia	+	∅	∅	∅	∅
Hypophosphatemia	++	++	+	∅	∅
Osteoporosis	±	±	∅	+++	∅
Malignancy	+	+	?	∅	+

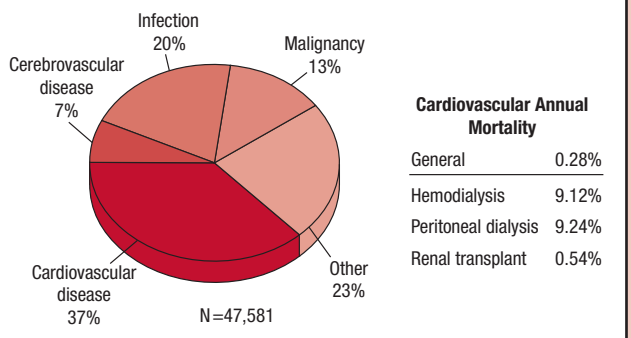
CsA = cyclosporine; Tac = tacrolimus; Srl = sirolimus; Ster = steroids; MMF = mycophenolate mofetil; +++ = severe; ++ = moderate; + = mild; ± = opposite; ∅ = none; ? = unknown.

Adapted from Martin Zand, MD.

Some recent studies may provide information in this regard. Serum Cr values were used to predict long-term renal transplant survival in one large analysis.[47] The results indicated that renal function at 1-year posttransplantation correlated with long-term graft survival. Additionally, patients experiencing acute rejection episodes during the first posttransplant year were more likely to develop functional damage to the kidney, and these individuals had worse outcomes than did those without rejection. Even among patients who experienced acute rejection, renal function was very important; the less the functional damage

FIGURE 3

MORTALITY IN RENAL TRANSPLANT RECIPIENTS



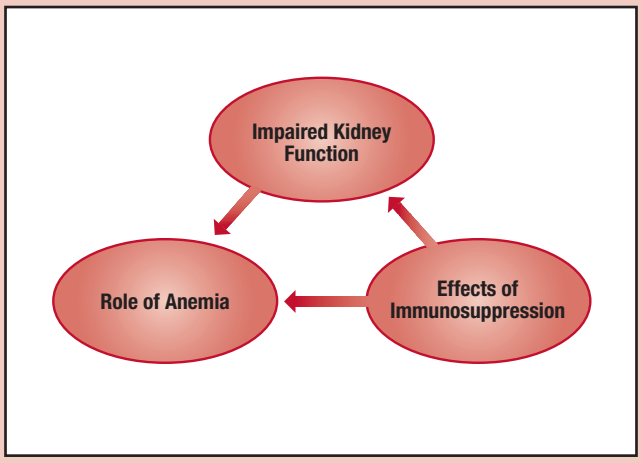
USRDS database, 2001.

Foley RN, et al. *J Am Soc Nephrol.* 1998;9(suppl 12):S16.

Foley RN, et al. *Am J Kidney Dis.* 1998;32(suppl 3):S112.

FIGURE 4

INTERPLAY BETWEEN ANEMIA, IMMUNOSUPPRESSION, AND IMPAIRED RENAL FUNCTION IN RENAL TRANSPLANT RECIPIENTS



to the kidney, the better the patient outcome after rejection. Similarly, when absolute creatinine levels were analyzed, it was shown that renal function during the first year posttransplantation was predictive of long-term graft survival (Figure 5).[48]

Another study used prediction diagnostics to evaluate whether deteriorating renal function was predictive of graft loss, death-censored graft loss, and patient death. The patient population was composed of primary transplant recipients from the USRDS database (after 1988) and included only those patients with ≥7 years of follow-up.[47] Patients were divided into 2 groups—those with SCr levels ≥1.6 mg/dL and those with SCr levels <1.6 mg/dL. The number of patients in each group who experienced graft loss was evaluated, as shown in Table 6, and the sensitivity and specificity were calculated. Sensitivity was approximately 62% and specificity approximately 55%; thus, about 40% of the time, the prediction would not be correct. Although sensitivity may be increased by changing the SCr cutoff levels, the caveat is that with such an increase, specificity decreases.

Sensitivity-specificity analyses showed that the predictive value remained essentially the same, approximately 62%. Thus, either SCr levels are not predictive of graft loss or there are other variables that may yield more substantive results. If more variables are added to the analyses (eg, anemia, homocysteine), it is possible that the fit of the above analyses would improve, as would the predictive value of the model. On the other hand, it may be that we have not yet found the best predictor of graft loss, and further studies may be necessary.

Despite these observations, SCr, although it may not predict patient and graft survival adequately on its own, remains one of the most critical and possibly one of the most important variables in assessing the risk of graft loss, patient death, and cardiovascular death.

MODIFIABLE FACTORS AS TARGETS FOR PRESERVING RENAL FUNCTION AFTER TRANSPLANTATION

"Because acute rejection consistently correlates with allograft arteriosclerosis and chronic allograft nephropathy and because graft vascular disease is mediated at least in part by T_H1 cytokines, modifications of such cytokines may represent a strategy to improve graft survival."

Marc I. Lorber, MD

The relationship between acute allograft rejection and long-term renal dysfunction provides important clues to strategies for improving late posttransplant outcomes. Donor age was identified in the 1970s by Cecka and Terasaki as an important contributor to long-term outcome. Renal transplants from older donors were associated with an increased risk of delayed graft function (DGF), and DGF was associated with increased rates of early and more severe acute rejection.[49] These observations have been regularly corroborated and have withstood the test of time. Addressing that very point, it was observed that optimal immunosuppression was critical in promoting satisfactory graft function and overcoming acute rejection during the first year posttransplantation.[50]

Recently, a risk index was established, seeking to predict the development of DGF after renal transplantation. The index was based on data from the USRDS database of 20,704 cadaveric renal transplants from January 1995 to June 1997. The most important characteristics were found to be donor age, cold ischemia time, recipient race, previous kidney transplant, and cause of donor death. DGF for any reason was found to reduce allograft survival (77%) compared with allograft survival in the absence of DGF (94%).[51]

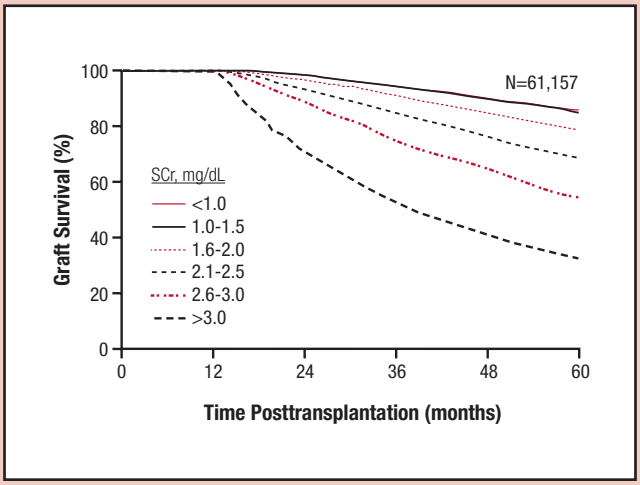
Strategies to improve renal allograft survival focus on minimizing negative consequences in several key areas: alloimmune activation, ischemia and reperfusion, and donor and recipient comorbidities. Regarding ischemia and reperfusion, the most important elements appear to be improving donor management, reducing cold ischemia time, and minimizing the negative consequences of revascularization. Unfortunately, there is little that can be done to modify donor and recipient comorbidities. However, approaches using modified methods of immunosuppression are desirable, particularly since newer agents have become available that offer attractive possible alternatives.

The exact etiology of chronic allograft rejection remains incompletely understood. Chronic allograft nephropathy is associated with particular histopathologic features, including arterial injury characterized by myointimal expansion with progressive remodeling, leading to luminal narrowing and, eventually, obliteration. These findings may explain the associated late interstitial fibrosis, perhaps ischemic in etiology, leading to late renal dysfunction and eventually transplant failure.

Among hypotheses possibly explaining the link between acute rejection and later development of chronic graft arteriopathy is the observation that acute vascular rejection is poorly managed by current therapeutic strategies. Accordingly, experimental models have focused on acute intimal arteritis resulting from immune effector cell interactions with the arterial endothelium and the possible linkage between these acute events as a precursor to the arterial lesion associated with chronic rejection (graft arteriosclerosis). Graft arteriosclerosis may also be a consequence of ischemia and absent or delayed reperfusion.

FIGURE 5

POSTTRANSPLANT RENAL FUNCTION IN THE FIRST YEAR PREDICTS LONG-TERM KIDNEY TRANSPLANT SURVIVAL



Reprinted with permission from Hariharan S, et al. *Kidney Int.* 2002;62:311-318.

TABLE 6

PREDICTION DIAGNOSTICS BASED ON NUMBER OF PATIENTS WITH OR WITHOUT GRAFT LOSS FOLLOWING TRANSPLANTATION

		Serum Creatinine ≥ 1.6 mg/dL	Serum Creatinine <1.6 mg/dL	Total
Graft loss	Yes	9,939	6,054	15,993
	No	8,710	10,552	19,262
Total (column)		18,649	16,606	35,255

Kaplan B, et al. *Am J Transplant*. 2003;3:1560-1565.

Several experimental models, one using the immunodeficient SCID mouse to study lymphoid, arterial interactions, have observed a reduction in the incidence and severity of intimal arteritis in the presence of cyclosporine and sirolimus.[52,53] Other studies using nonhuman primates found that high-dose sirolimus alone was able to arrest the progression of myointimal expansion in a cynomolgus aortic allograft model.[54] Experimental studies have also suggested that proinflammatory cytokines, including interferon-gamma, may provide an attractive target for modifying allograft vascular injury.[55,56]

The growing experience using TOR inhibitors in transplantation has provided promising results, with excellent efficacy, a tolerable safety profile, and the promise that this class of immunosuppressants may provide an important approach to limit the consequence of allograft arterial injury. The incidence of acute rejection using sirolimus-based regimens appears to approach 10%, and early difficulties with renal dysfunction seem controlled when lower doses of cyclosporine or tacrolimus are used with higher trough sirolimus concentrations in the 10 to 20 ng/mL range.[57] Other clinical results using rapamycin-impregnated coronary stents demonstrated a reduction in neointimal expansion and a reduced incidence of restenosis,[58] and a reduction in the maximal intimal thickness and cardiac transplant vasculopathy was observed using intravascular ultrasound among cardiac transplant recipients treated with the related TOR inhibitor everolimus.[59]

Accumulating evidence consistently associates the incidence of acute rejection with later development of allograft vasculopathy, and evidence supports the postulate that chronic allograft arterial disease is an important factor in long-term allograft failure. Among the more recently introduced immunosuppressive agents, the TOR inhibitors, including sirolimus and everolimus, have been associated with low rates of acute rejection and an excellent efficacy and favorable safety profile. Additionally, these agents may provide a strategy leading to amelioration of allograft vasculopathy, representing a potentially important strategy in improving long-term outcomes. Finally, experimental results indicating that graft vascular disease is mediated at least in part by T_H1 cytokines suggest that neutralization of these cytokines, such as interferon-gamma, may provide another promising approach toward the goal of improving long-term outcomes after transplantation.

IMPLICATIONS OF PRESERVING LONG-TERM RENAL FUNCTION AFTER RENAL TRANSPLANTATION

"Current regimens have improved renal function by reducing mean serum creatinine levels to about 1.3 mg/dL."

Stuart M. Flechner, MD

With the increasing number of individuals on kidney transplant waiting lists, we are faced with a high demand for organs that remain in limited supply. In addition, allograft nephropathy and the resulting graft loss compound the need for new organs. Furthermore, permanent renal failure is a growing problem encountered by long-term recipients of extrarenal organ transplants.[60]

One approach to this supply-and-demand problem is to concentrate on increasing graft survival and thus decrease the need for new organs. Unfortunately, although 1-year graft survival is excellent (88% to 94%), 5-year graft survival is not (63% to 76%).[61] Ten-year actuarial graft survival data are not available for the United States. In a Spanish study, patients were followed for at least 10 years, beginning when cyclosporine was the primary immunosuppressive agent in use. The cyclosporine-based regimen was compared with an azathioprine-based regimen.[62] The study showed a graft survival advantage with cyclosporine for the first 3 years (~25%); however, beyond 3 years the survival rate was not different between the 2 groups. If patients with severe infections, steroid-resistant acute rejection, surgical problems, early MIs, and other severe comorbidities were removed from the analysis, long-term outcomes were equivalent for the 2 groups. The authors concluded that loss of cyclosporine superiority was due to an increase in graft losses caused by chronic allograft nephropathy.

Currently, the most common immunosuppressive regimens generally include at least 3 drugs: an antilymphocytic agent (usually a calcineurin inhibitor), an antiproliferative agent (often mycophenolate mofetil), and steroids. With such a combination, 1-year acute rejection rates for cadaveric-organ recipients have been about 30%. With the addition of a depleting or nondepleting anti–T–cell antibody, there is a further reduction in acute rejection, with rates often <20% (Table 7, page 10).[63,64] Unfortunately, chronic rejection rates remain high.

The risk factor most strongly associated with chronic rejection, or chronic allograft nephropathy, appears to be early renal dysfunction (SCr levels >2 mg/dL at 6 months posttransplantation).[65] Hariharan and colleagues found that for every 0.5-mg/dL rise in mean 6-month creatinine, approximately 2 to 3 years of graft half-life are lost.[48] They observed that chronic allograft nephropathy can be reduced by as much as 50% if SCr levels are controlled after the 6-month time point.

Another known risk factor is nephrotoxicity, with which several immunosuppressive agents have been associated. During acute toxicity, tacrolimus and cyclosporine appear to increase the expression of fibrogenic genes.[66] Histologically, some form of chronic allograft nephropathy may be present in most patients receiving tacrolimus or cyclosporine at 2 years posttransplantation, even in those with relatively good renal function (mean SCr 1.5-1.6 mg/dL).[67] Unfortunately, when followed over a 10-year period, virtually all transplanted kidneys treated with calcineurin inhibitors demonstrate chronic allograft nephropathy on protocol biopsies.[68]

TABLE 7

RENAL TRANSPLANTATION OUTCOMES WITH CURRENT IMMUNOSUPPRESSIVE DRUG REGIMENS

	1-Year Acute Rejection Rate (%)	
Agent	**Without Ab Induction**	**With Ab Induction**
Aza + Pred	80	50-60
CsA + Pred	50-60	—
Tac + Pred	45	—
MMF + Pred	—	50
CsA + Aza + Pred	50	45
CsA + MMF + Pred	40	10-20
Tac + MMF + Pred	35	10-20

Ab = antibody; Aza = azathioprine; Pred = prednisone; CsA = cyclosporine; MMF = mycophenolate mofetil; Tac = tacrolimus.

Keown P, et al. *BioDrugs*. 2003;17:271-279.
Brennan DC, et al. *Transplantation*. 1999;67(7):1011-1018.

New Approaches to Immunosuppression

Several new therapeutic approaches have been implemented to promote long-term graft survival:

- **Drug avoidance**, in which there is the intentional avoidance of a drug with an undesired side effect
- **Drug elimination**, in which a specific drug is removed at a predetermined time to reduce its deleterious effect
- **Drug substitution**, in which alternative agents are used to keep the total amount of immunosuppression the same

With these approaches, newer drugs such as TOR inhibitors have been used, since these agents do not exhibit any evidence of nephrotoxicity. However, the results of drug-elimination and drug-substitution studies should be evaluated carefully before conclusions are based on them to ensure that there is fair distribution of patients and treatment options over a sufficient length of time.

Studies to evaluate calcineurin inhibitor–free immunosuppression have reported mixed outcomes. The interleukin-2 receptor blocker daclizumab was added to mycophenolate mofetil and prednisone in the absence of any calcineurin inhibitor and compared with immunosuppression containing a calcineurin inhibitor.[69] Although 1-year graft survival was good (96%), the acute rejection rate was unacceptably high (53%) in this study. In a study that used the drug-elimination approach to avoid nephrotoxicity, cyclosporine that had initially been combined with sirolimus and prednisone was discontinued after approximately 3 months.[70] At 2 years, patients who had discontinued cyclosporine (n=215) had significant improvements in renal function ($P<.001$), with SCr levels of 1.62 mg/dL, compared with 1.95 mg/dL in those who remained on cyclosporine (n=215).

Several substitution studies have directly compared calcineurin inhibitor therapy with calcineurin inhibitor–free regimens. The pooled results of 2 such studies show that treatment without calcineurin inhibitors improved GFR by approximately 20% compared with cyclosporine-containing regimens ($P=.004$).[71] Long-term SCr improvements also have occurred with monoclonal antibodies for induction. A randomized trial using basiliximab induction and maintenance therapy with mycophenolate mofetil and prednisone compared sirolimus with cyclosporine. Patient and graft survival (97% vs 100% and 97% vs 96%, respectively) were good in both groups. In addition, acute rejection rates were extremely low (2/31 vs 5/30, 6.5% vs 16.7%, respectively).[72] Notable differences in SCr levels were observed. Whereas the majority of patients taking cyclosporine had elevated mean SCr levels (≥1.8 mg/dL), mean SCr levels with sirolimus remained <1.4 mg/dL.

The combination of sirolimus and mycophenolate mofetil is the subject of increasing research interest. In a rat model of chronic rejection, this combination specifically inhibited vascular fibrous intimal thickening, allograft glomerulopathy, and interstitial fibrosis, effects that were not seen with either agent alone.[73]

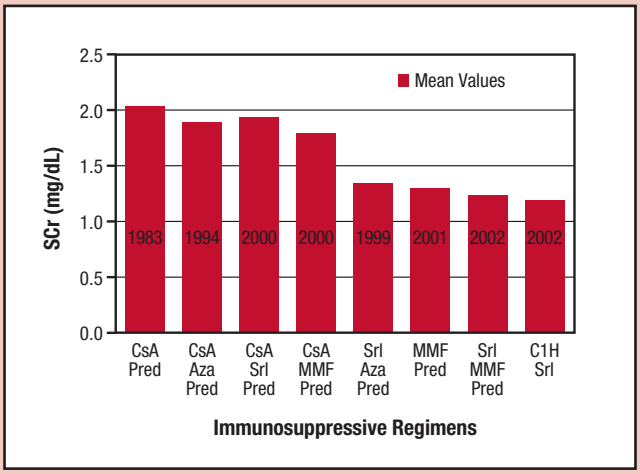
There have been several attempts over the years to preserve long-term renal function by varying the combination of immunosuppressive agents, as shown in Figure 6.[69,72,74-79] Current immunosuppressive regimens have improved renal function by reducing mean SCr levels. It remains to be determined whether such reductions translate into long-term kidney preservation and graft survival beyond 5 years.

CONCLUSION

Renal transplant recipients often have comorbidities, such as hypertension and diabetes, that exacerbate both renal and cardiovascular risk. Because these patients are at such high risk for morbidity and mortality, the search for a means of modifying their risk is of paramount importance. Many of the traditional and nontraditional risk factors are modifiable, and careful attention both to cardiac risk and preservation of renal function is likely to be crucial to patient management.

FIGURE 6

RENAL FUNCTION AT 1 YEAR POSTTRANSPLANTATION WITH VARIOUS IMMUNOSUPPRESSIVE REGIMENS



CsA = cyclosporine; Pred = prednisone; Aza = azathioprine; Srl = sirolimus; MMF = mycophenolate mofetil; C1H = Campath-1H.

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IMPLICATIONS FOR PRESERVING LONG-TERM RENAL FUNCTION AFTER RENAL TRANSPLANTATION

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Program Exam (*Please circle the correct answer*)

1. Kidney disease is defined by the Kidney Disease Outcomes Quality Initiative as a GFR of _____ mL/min for ≥3 months.
   a. <40
   b. <50
   c. <60
   d. <70

2. In a recent study among Medicare patients ≥67 years of age, the 1-year incidence of cardiovascular disease among patients with chronic kidney disease was _____ that of those not diagnosed with kidney disease.
   a. higher than
   b lower than
   c. not different from

3. Reductions in GFR result in:
   a. elevated systolic blood pressure
   b. increased levels of total cholesterol
   c. increased incidence of diabetes
   d. all of the above

4. Renal insufficiency has been shown to affect factors in the development of the metabolic syndrome.
   a. True
   b. False

5. According to Banff '97, the primary criteria for rejection are:
   a. tubulitis and glomerulitis
   b. interstitial inflammation and arteritis
   c. arteritis and tubulitis

6. Which of the following comorbidities is the leading cause of long-term mortality among kidney transplant recipients?
   a. cerebrovascular disease
   b. infection
   c. malignancy
   d. cardiovascular disease

7. Cardiovascular disease risk among kidney transplant recipients is _____ those of wait-listed patients with end-stage renal disease on dialysis.
   a. higher than
   b. lower than
   c. the same as

8. According to data reported by Hariharan et al, renal function in the first year post-transplantation is _____ correlated with long-term kidney allograft survival.
   a. directly
   b. inversely
   c. not

9. Which of the following statements is (are) true?
   a. Acute rejection consistently correlates with later allograft arteriosclerosis and chronic allograft nephropathy.
   b. Proinflammatory cytokines, such as interferon-gamma, are not mediators of graft arteriosclerosis.
   c. TOR inhibitors, such as sirolimus, are associated with excellent patient and graft survival with low acute rejection rates.
   d. a and c
   e. All of the above

10. Based on USRDS data, the most important factors in the development of delayed graft function include:
    a. donor age
    b. cold ischemia time
    c. previous kidney transplant
    d. a and c
    e. All of the above

11. A recent drug-avoidance study among renal allograft recipients receiving basiliximab induction and either sirolimus or cyclosporine showed that:
    a. 1-year transplant outcomes were better in the cyclosporine group
    b. 1-year transplant outcomes were better in the sirolimus group
    c. patients on cyclosporine had better renal function at 1 year posttransplantation
    d. patients on sirolimus had better renal function at 1 year posttransplantation

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Please circle the number that best reflects your opinion of the following statements, using the following rating scale:

1 = Strongly Agree; 2 = Agree; 3 = Disagree; 4 = Strongly Disagree

1. The program objectives were met.	1	2	3	4
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3. The program was educational and not promotional.	1	2	3	4
4. The program will change the way I practice.	1	2	3	4
5. The authors demonstrated expertise in the topic.	1	2	3	4
6. The material was presented at an acceptable level of expertise.	1	2	3	4
7. The information presented was without promotional or commercial bias.	❑ Agree		❑ Disagree	

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